Small Intestinal Bacterial Overgrowth

A Framework for Understanding Irritable Bowel Syndrome

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Context Irritable bowel syndrome (IBS), which affects 11% to 14% of the population, is a puzzling condition with multiple models of pathophysiology including altered motility, visceral hypersensitivity, abnormal brain-gut interaction, autonomic dysfunction, and immune activation. Although no conceptual framework accounts for all the symptoms and observations in IBS, a unifying explanation may exist since 92% of these patients share the symptom of bloating regardless of their predominant complaint.

Evidence Acquisition Ovid MEDLINE was searched through May 2004 for relevant English-language articles beginning with those related to bloating, gas, and IBS. Bibliographies of pertinent articles and books were also scanned for additional suitable citations.

Evidence Synthesis The possibility that small intestinal bacterial overgrowth (SIBO) may explain bloating in IBS is supported by greater total hydrogen excretion after lactulose ingestion, a correlation between the pattern of bowel movement and the type of excreted gas, a prevalence of abnormal lactulose breath test in 84% of IBS patients, and a 75% improvement of IBS symptoms after eradication of SIBO. Altered gastrointestinal motility and sensation, changed activity of the central nervous system, and increased sympathetic drive and immune activation may be understood as consequences of the host response to SIBO.

Conclusions The gastrointestinal and immune effects of SIBO provide a possible unifying framework for understanding frequent observations in IBS, including postprandial bloating and distension, altered motility, visceral hypersensitivity, abnormal brain-gut interaction, autonomic dysfunction, and immune activation.

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IRRITABLE BOWEL SYNDROME (IBS) IS a common diagnosis that affects 11% to 14% of the population.[1,2] Currently, IBS is a diagnosis made on the basis of meeting clinical criteria.[3-6] This symptom-based approach has been used because no consistent biological marker or unifying framework has been available to explain the different symptoms and findings of IBS. The varying symptoms in IBS have led to efforts looking at differences rather than similarities between patients.[6]

Another way we have emphasized the difference rather than the similarity is in the grouping of one set of symptoms of these patients as IBS and another set of symptoms as belonging to some other diagnosis. The clinical criteria for IBS do not include the extraintestinal symptoms that are common in these patients such as fatigue or myalgia. Instead, these complaints are viewed as symptoms of other diagnoses that coexist with IBS such as chronic fatigue syndrome[7] and fibromyalgia.[8] This separation may be an artifact of medical specialization.[9] As such, a unifying framework for understanding IBS that could account for both the gastrointestinal as well as the extraintestinal symptoms of these patients would warrant serious consideration.

EVIDENCE ACQUISITION

Ovid MEDLINE was searched through May 2004 for articles using combinations of the terms *bloating*, *gas*, *IBS*, *postinfectious IBS*, *small intestinal bacterial overgrowth* (SIBO), *microbial translocation*, *bacteria*, *visceral hypersensitivity*, *immune response*, *autonomic dysfunction*, *central nervous system*, *intestinal motility*, *fibromyalgia*, *chronic fatigue syndrome*, *interstitial cystitis*, *lactulose and glucose breath test*, and *sickness behavior*. Additional sources were identified by scanning through the bibliographies of articles and books. Publications reviewed ranged from randomized controlled trials to case-control studies. Although randomized controlled trials were considered to be the strongest evidence, such studies were few, so the evidence was considered to be most compelling when there was consistency among the results of multiple different studies. Quality of data was assessed by publication in a peer-reviewed journal. A few critical recent abstracts were also considered.

EVIDENCE SYNTHESIS

Postprandial Bloating as a Unifying Symptom of IBS

Regardless of whether an IBS patient is troubled predominantly by constipa-

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tion, diarrhea, or pain, 92% of IBS patients complain of bloating and pain, with 89% having a bloating score of 5 or greater (out of 10).[10] Although many IBS patients describe worsening of their symptoms by food intake,[11] most are unsuccessful in identifying a food trigger.[12] This extremely common complaint of postprandial bloating[4] supports the possibility of a unifying pathophysiology. This symptom is associated with abdominal distension and has been corroborated by direct physical evidence of increased intestinal gas as measured by abdominal films,[10,13] computed tomography of the abdomen,[14] and plethysmographic measurement showing increased abdominal girth at the end of the day but decreased girth overnight after fasting.[15,16] The possibility of a unifying explanation for IBS is further supported by reproducible x-ray findings of Koide et al[13] in which increased intestinal gas was noted regardless of bowel movement pattern. Of note, the increased gas was localized to the small rather than the large intestine.

Intestinal Gas Excretion Is Greater in IBS

Although in some studies intestinal gas volume of IBS patients has been reported to be no different than that of healthy controls,[17,18] the gas measurement in these studies was done in a fasting state. As such, no conclusion can be drawn from these studies regarding meal-induced bloating in IBS patients. In contrast, both total hydrogen production (median, 332 vs 162 mL) and maximal rate of gas excretion (2.4 mL/min vs 0.6 mL/min) were greater following lactulose ingestion in IBS patients (6 subjects) than healthy controls.[19] This finding of a 4-fold greater rate of maximal gas excretion and greater total hydrogen excretion provided direct evidence of increased gas production in IBS in the presence of a fermentable substrate. Since the excreted gases were hydrogen and methane, this abnormal response to lactulose in IBS patients cannot be explained by a disaccharide intolerance.[20] This group reported similar findings in another study where the 24-hour total excretion of hydrogen following lactulose was substantially greater in IBS patients (median, 333.7 mL/24 h; interquartile range, 234.7-445.67 mL) than in normal volunteers (median, 203.1 mL/24 h; interquartile range, 131.4-256 mL; $P=.002$) or IBS patients who failed exclusion diet (median, 204 mL/24 h; interquartile range, 111.35-289.13 mL; $P=.02$).[21] Current construct models of the pathophysiology of IBS, including abnormal motility,[22] visceral hypersensitivity,[23] altered brain-gut interaction,[24] autonomic dysfunction,[25] and immune activation,[26] do not account for the nearly universal symptom of postprandial bloating, the physical evidence of increased intestinal gas that is localized to the small intestine, the effect of probiotics on bloating,[27] or the increased gas excretion after lactulose ingestion.[19,21]

Normal Intestinal Gas Production

From the seminal work of Levitt,[28] we know that the site of hydrogen production by bacterial fermentation is limited to the distal gut. The duodenum and jejunum are often sterile, and the proximal ileum may be sterile. The concentration of gut bacteria drops precipitously from 10^{10-12} organisms per mL in the cecum to 10^{5-8} organisms per mL in the terminal ileum, 10^{0-5} in the proximal ileum, and 10^{0-4} in the jejunum and the duodenum.[29-31] For fermentation to begin, food must reach these distal gut bacteria. In the normal state, the digestibility of dietary starch is the primary determinant of how much bacterial fermentation takes place in the gut (FIGURE 1).[32] The elimination of the hydrogen produced by bacterial fermentation depends significantly on methanogenic and sulfate-reducing bacteria that convert hydrogen to methane and hydrogen sulfide.[33] These organisms are highly competitive so that the stool of an individual contains high concentrations of only 1 of these 2 types of organisms.

If Not the Food, the Problem May Be the Bacteria

Since no specific food intolerance can explain the greater increase in hydrogen excretion after lactulose ingestion,[19] the abnormal fermentation problem may not be the food but rather, the gut bacteria. If food is not moving down to the bacteria, then bacteria may be moving to the site of food assimilation for fermentation and gas production to take place. SIBO describes just such proximal expansion of gut bacteria (Figure 1) and provides a biologically plausible framework for the bloating of IBS. What evidence is there to support the role of bacterial overgrowth in IBS?

Prevalence of SIBO and Effect of Antibiotic Treatment in IBS

In a study of 202 patients meeting Rome I criteria for IBS by Pimentel et al,[34] an abnormal breath test result suggesting SIBO was found in 78%. In this uncontrolled study, when the second breath test result after antibiotic treatment became normal, consistent with successful eradication of bacterial overgrowth, symptoms were reduced enough so that only half of the patients still met clinical criteria for IBS. The possibility of bacterial overgrowth as a unifying framework for understanding the symptoms of IBS patients is further supported by reduction of both gastrointestinal and extraintestinal symptoms when eradication of SIBO was achieved.[34] However, it is not clear at this time whether alteration of colonic bacterial flora by antibiotics may also play a role in symptom improvement.

These findings were then corroborated by a double-blind, randomized, placebo-controlled study by Pimentel et al[35] where 111 patients were drawn from the general IBS population, with no a priori selection on the basis of chief complaint. The prevalence of abnormal lactulose breath test result in this controlled study was 84% vs 20% in the control subjects who did not meet Rome I criteria (odds ratio, 26.2; 95% confidence interval, 4.7-103; $P<.001$). There was a graded effect of treatment whereby the mean

(SE) normalization of global symptoms within 1 week of randomization was 11.0% (3.7%) for placebo-treated patients, 36.7% (6.1%) for antibiotic-treated patients who did not achieve bacterial eradication, and 75.0% (6.4%) for antibiotic-treated patients who also achieved bacterial eradication ($P<.001$, 1-way analysis of variance). This graded response is consistent with an antibiotic-sensitive pathophysiology of IBS. A similar study consistency was demonstrated by a double-blind, placebo-controlled study that showed metronidazole to be superior to placebo in relieving symptoms in IBS patients,[36] while another recent report by Nucera et al[37] showed that 75% of 200 IBS patients have an abnormal lactulose-glucose breath test result consistent with the presence of SIBO.

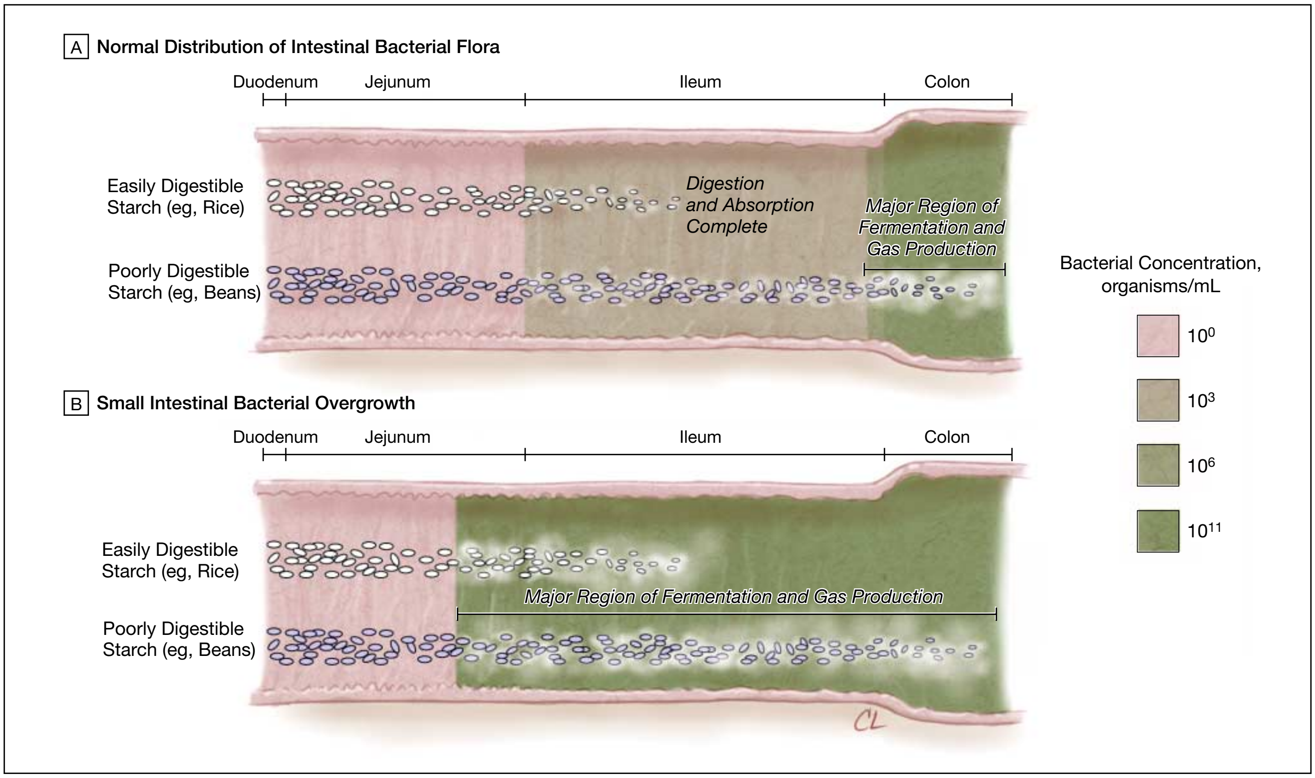
The Type of Gas May Contribute to Constipation

If SIBO provides a unifying framework for understanding IBS patients, how does this account for the possibility of both constipation and diarrhea? The type of gas produced by gut bacteria may be an important factor. In 2 studies by Pimentel et al,[35,38] excretion of methane alone was only found in constipation-predominant IBS patients. Methane as a gas slows intestinal transit[39] and reduces postprandial plasma level of serotonin,[40] the mediator of the peristaltic reflex.[41] Methane excretion has been found in 65% of children with encopresis compared with 15% of the control patients.[42] A role for gut bacteria as one of the factors in constipation is further suggested by the observation in 8 patients with chronic idiopathic constipation that stool frequency and consistency improved after a 14-day course of antibiotics.[43]

Abnormal Small Intestinal Motility May Explain SIBO in IBS

Between meals, the interdigestive motility of the upper gastrointestinal tract is characterized by a cyclical pattern of activity known as the major migrating complex (MMC).[44] The MMC includes a period of powerful, lumen-obliterating contractions that propagates from the stomach or duodenum distally to the terminal ileum (phase III of MMC or the intestinal housekeeper wave).[44] When compared with recordings from healthy controls, the frequency of these intestinal housekeeper waves was significantly reduced in IBS patients,[45] which may also explain the abnormal gas retention that is observed in IBS patients.[18] The im-

Figure 1. Distribution of Intestinal Bacterial Flora in Normal Gut and in Small Intestinal Bacterial Overgrowth


A Normal Distribution of Intestinal Bacterial Flora
Duodenum
Jejunum
Ileum
Colon
Easily Digestible Starch (eg, Rice)
Poorly Digestible Starch (eg, Beans)
Digestion and Absorption Complete
Major Region of Fermentation and Gas Production
B Small Intestinal Bacterial Overgrowth
Duodenum
Jejunum
Ileum
Colon
Easily Digestible Starch (eg, Rice)
Poorly Digestible Starch (eg, Beans)
Major Region of Fermentation and Gas Production
Bacterial Concentration, organisms/mL
10^0
10^3
10^6
10^11
CL

A, In the normal gut, easily digestible starch undergoes complete digestion and absorption within the proximal small intestine and is not available for fermentation in the distal ileum and colon where bacterial colonization is the greatest.[29-31] In contrast, gas production results from bacterial fermentation of poorly digestible starch that is not assimilated by the proximal gut. B, In small intestinal bacterial overgrowth, the concentration of bacterial flora increases proximally allowing fermentation of both easily digestible and poorly digestible starches.

portance of the relationship between abnormal phase III of MMC and SIBO was first described by Vantrappen et al[46] in patients with organic gastrointestinal disorders and extended in animal and human studies to the relationship between small bowel motility and gut bacteria[47,48]; small bowel motility and SIBO[49]; and small bowel motility, SIBO, and bacterial translocation.[50]

Why Is Prevention of SIBO Important?

Bacterial translocation, a known complication of SIBO,[51] is the movement of gut bacteria from the lumen across the mucosal barrier.[52] In rats, experimentally induced SIBO leads to the appearance of gut bacteria in the mesenteric lymph nodes and visceral organs.[49] A potentially important consequence of bacterial translocation is immune activation. In a report of 11 patients, an increase in the number of intraepithelial lymphocytes was observed as mucosal evidence of this immune response to confirmed bacterial translocation.[53] This adverse outcome could explain why the normal gut has defensive mechanisms in place to keep the bacterial flora away from the small intestine, particularly the bowel proximal to the ileum.

Immune Activation Is Also Present in IBS

Mucosal evidence of an activated immune response has been reported recently in patients who develop IBS after recovering from acute gastroenteritis (postinfectious IBS)[54-56] and in those without such history.[57,58] Of the IBS population, 25% to 30% of patients have an antecedent history of acute gastroenteritis.[54,55,59] In these reports, postinfectious IBS patients have an increased number of intraepithelial lymphocytes,[59,60] just like the patient with documented bacterial translocation.[53]

An episode of acute gastroenteritis is not needed to explain immune activation in IBS. In a study of 77 IBS patients, an increase in the number of activated intraepithelial lymphocytes was found in almost 90% of the subjects regardless of the acuteness of their onset or their predominant gastrointestinal symptom.[26] The magnitude of the immune activation in patients without a history of acute gastroenteritis is, in fact, even more prominent than those with that history.[26] These observations have provided strong study consistency in support of the biological plausibility for a role of inflammation in IBS as proposed by Collins.[61-63] Any framework for understanding IBS must, therefore, account for these and other observations of immune activation.[26,54,57,59] The role of an underlying process that involves inflammation in IBS is further supported by observations of a genetic predisposition in some IBS patients to produce less anti-inflammatory products[64] or more pro-inflammatory products.[65] Although the trigger for the immune response in IBS has not been identified, SIBO would provide a framework for understanding the activated immune response in IBS. In postinfectious IBS patients, along with immune activation, there is also increased intestinal permeability,[59,66] which has a known association with SIBO in animals[67] and humans[68] as the experimental correlate of the "leaky gut syndrome."

Immune Response to Bacteria Explains Abnormal Motility and Visceral Hypersensitivity

Lipopolysaccharide, an endotoxin of gram-negative bacteria, accelerates intestinal transit.[69] This may be mediated by mast cell degranulation, immune activation, cytokine production, and the triggering of preprogrammed responses of the enteric nervous system, including hypersecretion and power peristalsis[70] leading to diarrhea and cramping abdominal pain. Visceral hypersensitivity has been reported as a characteristic of IBS.[23] The immune response to these bacterial products would also explain this finding. Lipopolysaccharide has also been reported to induce visceral hypersensitivity in rats.[71] Weston et al[72] proposed earlier that increased mast cells in the ileum of IBS patients might be linked to altered visceral perception.

Similar to IBS, Fibromyalgia May Also Be Explained by SIBO

It is well recognized that there is a high degree of overlap between IBS, fibromyalgia, interstitial cystitis, and chronic fatigue syndrome.[7,73,74] While interstitial cystitis[75] and IBS[23] are diagnoses associated with hypersensitivity at the level of the bladder and gut, respectively, fibromyalgia may be considered a kind of hypersensitivity at the musculoskeletal level.[73] Although the cause of the hypersensitivity in these disorders is not well understood, the striking overlap of hypersensitivity in these functional disorders suggests the possibility of a unifying explanation. In a study of patients meeting American College of Rheumatology criteria for fibromyalgia, an abnormal lactulose breath test result suggesting SIBO was found in 42 out of 42 patients.[38] Fibromyalgia patients had a higher breath hydrogen concentration than IBS patients. Thus, an abnormal breath test result suggesting SIBO may reflect a common pathophysiological link between fibromyalgia and IBS. The immune response to bacterial antigen in SIBO provides a framework for understanding the hypersensitivity in both fibromyalgia and IBS.

CONTROVERSIES

Diagnostic Approach to SIBO

Since direct culture is usually considered the gold standard for the diagnosis of a bacterial disease, the use of an indirect approach such as the lactulose breath test for the diagnosis of SIBO is controversial. When it comes to diagnosing SIBO, the problem with the direct approach is one of access. While bacterial overgrowth can occur only in the more distal portions of the 300- to 500-cm length of the small intestine,[76] direct aspiration and culture are limited by the reach of instrumentation. Since only the small intestine proximal to the ligament of Treitz is usually reached by an endoscope (~60 cm), there is a high false-negative rate with this approach for the diagnosis of SIBO.[77,78] Even with these limitations of access, Simren et al[79] reported that

4 (12%) of 33 IBS patients had more than 100 000 colony-forming units of bacteria of colonic origin in the duodenum. While the prevalence is considerably lower than that detected by lactulose breath testing,[34,35,37] this study provided direct confirmation of the expansion of colonic bacteria proximally all the way to the duodenum in some IBS patients. Using glucose instead of lactulose as the substrate for a breath test is similarly limited,[80] since glucose is rapidly absorbed with the fermentable substrate removed from the lumen of the upper small intestine. In contrast, since lactulose is poorly digestible, this fermentable substrate does remain available in the lumen for fermentation by gut bacteria anywhere along the gut (FIGURE 2).

Interpreting a Premature Rise of Breath Hydrogen

A premature rise of breath hydrogen is a feature of both bacterial overgrowth and excessively rapid transit. However, 2 observations point away from rapid transit as the primary explanation for the findings by Pimentel et al.[34,35] First, the time-to-rise of breath hydrogen normalized with successful eradication of SIBO by antibiotics in the IBS patients.[35] Second, the abnormal gas profiles of the constipation-predominant IBS (slow transit) patient overlapped with that of the diarrhea-predominant IBS patients (fast transit).

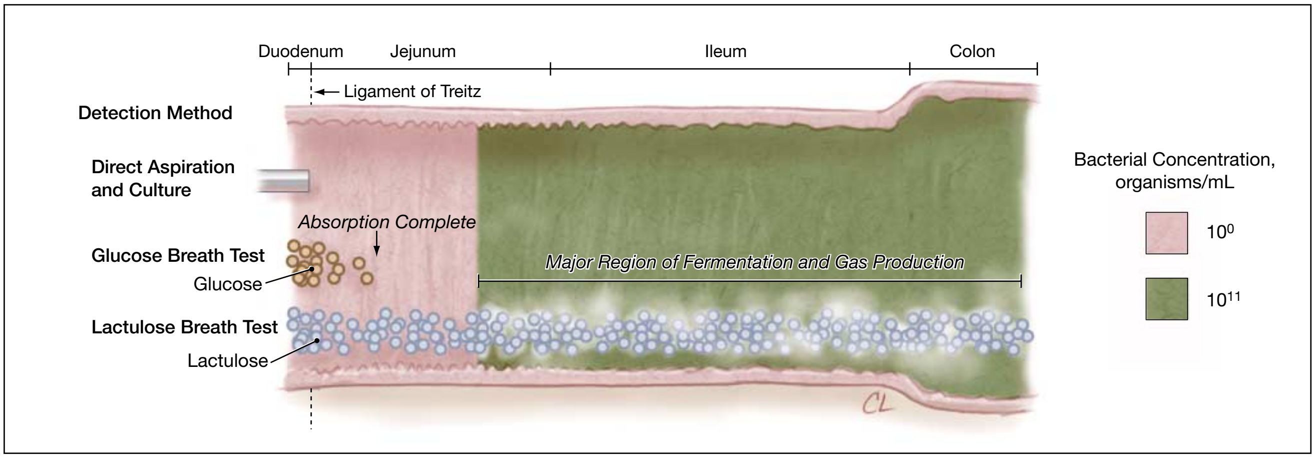
Role of Sugar Intolerance in IBS

There has been recent interest in fructose intolerance as a possible explanation for unexplained gastrointestinal symptoms.[20] Interestingly, there is a similar pattern of malabsorption in IBS patients across a number of tested fermentable substrates.[81] For many patients, the association between sugar intolerance and IBS may be related to bacterial overgrowth rather than true sugar intolerance. Nucera et al[37] found a high rate of disappearance of malabsorption to lactose (86.6%), fructose (97.5%), and sorbitol (90.9%) once SIBO was eradicated. Similarly, Pimentel et al reported that while the number of IBS patients with true lactose intolerance was low (16%), a much higher number (58%) had an abnormal lactose breath test result and there was a significant correlation between lactulose (SIBO) and lactose breath test result.[38]

Activated Immunity May Explain Altered Brain-Gut Interaction and Autonomic Dysfunction in IBS

Abnormalities of autonomic nervous system function, including disturbed sleep,[82] have been described in patients with IBS.[25] Using SIBO as a framework for understanding IBS, these neural changes can be understood on the basis of 2-way triggered communications between the immune system and the autonomic nervous system.[83] An example of this interaction is the defensive sympathetic response to stress involving immune activation of noradrenergic neurons.[84] Using a variety of brain imaging techniques, IBS patients have been observed to exhibit a different pattern of brain response to visceral stimuli than healthy control subjects.[24] Since inflammation in animal models leads to multiple changes in the brain, including activation of neurons as documented by Fos expression,[84,85] alteration of hypothalamic-pituitary-adrenal axis including elevation of corticotropin-releasing factor (CRF) concentration,[86] and change in neurotransmitter levels,[87] such altered brain-gut interactions may be a part of the systemic response to a

Figure 2. Regions of Intestine Accessible by Various Diagnostic Methods to Detect Small Intestinal Bacterial Overgrowth (SIBO)



Detection of SIBO depends on location of and access to bacterial flora. SIBO by culture is defined by bacterial concentration proximal to the distal ileum >10^5 organisms per mL. In this example of SIBO, the concentration of bacterial flora in the distal jejunum and ileum has increased to that typically present in the normal colon (10^{11} organisms per mL). Culture of intestinal flora sampled by direct aspiration, which commonly is able to access the duodenum, would not detect the region of increased bacterial flora in this example. Similarly, a breath test using glucose as the fermentable substrate would only detect bacterial flora in the duodenum and proximal jejunum because glucose is rapidly absorbed. In contrast, a breath test using lactulose, which is not absorbed by the intestine, would be able to detect bacterial flora anywhere along the gut.

trigger of inflammation. The immune response to bacterial antigens is known to lead to sickness behavior[88] including flu-like symptoms of fatigue, anxiety, depression,[89] and impaired cognition.[90] Within that framework, the psychological and psychiatric comorbidity that are so common in IBS[91] and the response of selected symptoms to cognitive-behavioral therapy or antidepressants[92] may be understood.

CONCLUSIONS

Given the marked variability of symptoms and findings in patients with IBS, multiple models of pathophysiology and varying treatment strategies have been proposed. In this review, the available observations on IBS were considered and synthesized in an attempt to achieve a goal of integration. In this effort, it is biologically plausible that the gastrointestinal and extraintestinal symptoms and findings of IBS have a single, unifying explanation. Specifically, SIBO provides a framework for understanding IBS by accounting for the following observations in IBS patients. Nearly all of the symptoms and findings of IBS are wholly consistent with SIBO, including postprandial bloating (which is nearly universal), physical evidence of small bowel gas irrespective of predominant symptoms, high prevalence of abnormal lactulose breath test results, dramatic reduction in symptoms when antibiotic therapy is given and breath tests subsequently normalize, altered gut motility, visceral hypersensitivity, abnormal brain-gut interactions, evidence of autonomic dysfunction, nearly uniform immune activation regardless of prior acute gastroenteritis, and extraintestinal symptoms that are often flu-like in quality.

As a unifying framework for understanding IBS and other functional disorders, SIBO provides a target for exciting research that may lead to better diagnostic and treatment approaches. SIBO is a condition characterized by a chronic relapsing clinical course.[76] Since indefinite use of antibiotics is not an attractive option, future research should be directed at understanding and controlling the interaction between host and gut bacteria.

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